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WILLIAM M. SMITH
TOWNSEND AND TOWNSEND KHOURIE AND CREW
STUART STREET TOWER
ONE MARKET PLAZA, 20TH FLOOR
SAN FRANCISCO, CA 94105

EXAMINER	
CHAMBERS, J	
ART UNIT	PAPER NUMBER

1804
DATE MAILED:

05/02/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS☐ This application has been examined ☒ Responsive to communication filed on 1/9/95 ☐ This action is made final.A shortened statutory period for response to this action is set to expire three (3) month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

- | | |
|---|--|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input checked="" type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input checked="" type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-28, 41-53, 55-95 and 97-127 are pending in the application.
Of the above, claims 1-28, 41-53, 55-72, 74-81, 84-95 are withdrawn from consideration.
2. ☒ Claims 29-40, 54, 96 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 73, 82, 83, 97-127 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

82, 83, 97-118, 123, 125, 126, 128**EXAMINER'S ACTION**

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Applicants' election without traverse of Group II, claims 73, 82, 83 and 97-127 in Paper No. 9, filed January 9, 1995 is acknowledged.

Claims 120-127, newly added, are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 120 depends on non-elected claim 1. It is suggested that claim 120 be re-written as an independent claim. In claims 122 and 123, it is not clear if the step of propagating the zygote to form an embryo is carried out in vitro.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the claimed invention and an enabling disclosure.

Claim 73 is directed to a transgenic bovine species capable of producing a recombinant polypeptide in saliva. While the specification discloses the preparation of a transgenic cow which expresses a recombinant polypeptide in mammary tissue, there is no written description of the preparation of a transgenic cow producing a recombinant polypeptide in saliva. There is also no guidance as to how to select regulatory gene sequences for expression and secretion in saliva. According, the specification fails to provide an adequate written description of the claimed invention and an enabling disclosure.

Claim 73 is rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 73, 82, 83, 97, newly amended, and claims 98-127, newly added, are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to the use of the transgenes specifically disclosed in the specification. See MPEP 706.03(n) and 706.03(z).

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The first paragraph of 35 U.S.C. 112 requires that the specification be enabling as of the effective filing date of the application for one skilled in the art to make and use the full scope of the invention being claimed. Moreover, the Court in In re Vaeck (20 USPQ 1438, Fed. Cir. 1991) held that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification.

In the instant case, the specification is not enabling for the use of all transgenes. While the claims are directed to the use of all promoter, enhancer and secretory sequences, or all mammary-gland specific promoter, enhancer and secretory sequences, the specification only teaches a transgene comprising transcriptional regulatory sequences from the bovine -s1 casein gene. The specification provides little or no guidance on how to isolate, select and screen for transgene constructs comprising all promoter, enhancer and secretory sequences, or all mammary-gland specific promoter, enhancer and secretory sequences. It is well known that the production of transgenic animals is a relatively new and unpredictable technology. It is also well known in the art that the level and the specificity of expression of a transgene as well as the phenotype of the transgenic animal thus produced are greatly dependent on the specific transgene construct used. The individual gene of interest, promoter, enhancer, coding or noncoding sequences present in the transgene construct, the site of integration, and methylation-inactivation of the transgene, etc., are all important factors in controlling the expression of a transgene. See Palmiter et al. which discusses the effects of introns on the expression of transgenes and Kappel et al. which discusses the effect of methylation-inactivation (the right column of page 549), for example. Thus, the phenotype and the utility of a transgenic animal can not be readily predicted. Indeed, the expression of the whey acidic protein in transgenic pigs impaired mammary development (Shamay et al.). Thus, in view of the lack of guidance provided by the specification and the unpredictability of the art, it would have required one skilled in the art undue experimentation to prepare transgenic bovine species using all promoter, enhancer and secretory sequences, or all mammary-gland specific promoter, enhancer and secretory sequences. Accordingly, the disclosure is enabling only for claims limited to the use of the transgenes specifically disclosed in the specification.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

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A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 120 and 121, newly added, are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over any one of Meade et al. ('316 patent), Hopp (B6) or Gordon et al. (EPA).

Meade et al., Hopp and Gordon et al. each discloses a method for producing a transgenic mammal capable of producing a human serum protein in the milk of the mammal. Each of these references also suggested that a number of mammalian species including cows can be readily produced by the disclosed methods (see column 2, lines 60-61 of Meade et al., page 13 and claims 9, 11 and 13 of Hopp, and page 4, lines 44-45 and claim 13 of Gordon et al.). It is noted that the steps recited in the claimed method are generally applicable to all mammalian species. Accordingly, Applicants' claimed invention is anticipated by any one of the references. If, in fact, Applicants' claimed method is not identical to those disclosed by the references, it would still have been obvious for one of ordinary skill in the art to modify or optimize any one of the disclosed methods for producing a transgenic bovine, using routine experimentation. Thus, the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

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Claims 122-127, newly added, are rejected under 35 U.S.C. 103 as being unpatentable over any one of Meade et al. ('316 patent), Hopp (B6) or Gordon et al. (EPA), when taken with First et al. ('979 patent).

Meade et al., Hopp and Gordon et al. each discloses a method for producing a transgenic mammal capable of producing a human serum protein in the milk of the mammal. Their teachings differ from the claimed invention in that they do not specifically teach the preparation of a transgenic cow or the in vitro fertilization and culturing of bovine ova into implantable embryos. However, each of these references suggested that a number of mammalian species including cows can be readily produced by the disclosed methods (see column 2, lines 60-61 of Meade et al., page 13 and claims 9, 11 and 13 of Hopp, and page 4, lines 44-45 and claim 13 of Gordon et al.). Furthermore, at the time the claimed invention was made, First et al. had disclosed a method of in vitro fertilizing and culturing bovine ova into implantable embryos (see column 9, lines 59-63, for example). Accordingly, it would have been obvious for one of ordinary skill in the art to modify the teachings of any one of Meade et al., Hopp or Gordon et al. by introducing a human serum protein gene into bovine embryos which have been fertilized in vitro in order to obtain transgenic cows capable of producing a human serum protein in their milk, with a reasonable expectation of success. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C.103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). Thus, the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Claims 73, 82, 83, 97, newly amended, and claims 98-121, newly added, are rejected under 35 U.S.C. 103 as being unpatentable over any one of Meade et al. ('316 patent), Hopp (B6) or Gordon et al. (EPA), when taken with any one of Loskutoff et al. (C37), Biery et al. (C31) or Bondioli et al. (C32).

Meade et al., Hopp and Gordon et al. each discloses a method for producing a transgenic mammal capable of producing a human serum protein in the milk of the mammal. Their teachings differ from the claimed invention in that they do not specifically teach the preparation of a transgenic cow. However, each of these references suggested that a number of mammalian species including cows can be readily produced by the disclosed methods (see column 2, lines 60-61 of Meade et al., page 13 and claims 9, 11 and 13 of Hopp, and page 4, lines 44-45 and claim 13 of Gordon et al.). Furthermore, at the time the claimed invention

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was made, Loskutoff et al. and Biery et al. each had disclosed a method of gene transfer in bovine embryos and Bondioli et al. had taught the production of transgenic cattle. Accordingly, it would have been obvious for one of ordinary skill in the art to modify the teachings of any one of Meade et al., Hopp or Gordon et al. by introducing a human serum protein gene into bovine embryos as taught by any one of Loskutoff et al., Biery et al. or Bondioli et al. in order to obtain transgenic cows capable of producing a human serum protein in their milk, with a reasonable expectation of success. Thus, the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Claims 122-127, newly added, are rejected under 35 U.S.C. 103 as being unpatentable over any one of Meade et al. ('316 patent), Hopp (B6) or Gordon et al. (EPA), when taken with any one of Loskutoff et al. (C37), Biery et al. (C31) or Bondioli et al. (C32), as applied to claims 73, 82, 83, 97 and 98-121 above, and further in view of First et al. ('979 patent).

At the time the claimed invention was made, First et al. had disclosed a method of in vitro fertilizing and culturing bovine ova into implantable embryos (see column 9, lines 59-63, for example). Accordingly, the additional modifications of the teachings of any one of Meade et al., Hopp or Gordon et al. by employing bovine zygotes fertilized in vitro for gene transfer and subsequently culturing the transgenic bovine zygotes into implantable embryos would have been obvious to one of ordinary skill in the art. Thus, the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Claims 73, 82, 83, 97, newly amended, and claims 98-121, newly added, are rejected under 35 U.S.C. 103 as being unpatentable over any one of Simons et al. (C38), Clark et al. (C35), Gordon et al. (C36) or Bremel et al. (C34), when taken in view of any one of Loskutoff et al. (C37), Biery et al. (C31) or Bondioli et al. (C32).

Simons et al., Clark et al. and Gordon et al. each discloses a method for producing a transgenic mammal capable of producing a human serum protein in the milk of the mammal while Bremel et al. review methods for producing recombinant proteins in the milk of transgenic mammals. Their teachings differ from the claimed invention in that they do not specifically teach the preparation of a transgenic cow. However, at the time the claimed invention was made, Loskutoff et al. and Biery et al. each had disclosed a method of gene transfer in

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bovine embryos and Bondioli et al. had taught the production of transgenic cattle. Accordingly, it would have been obvious for one of ordinary skill in the art to modify the teachings of any one of Simons et al., Clark et al., Gordon et al. or Bremel et al. by introducing a human serum protein gene into bovine embryos as taught by any one of Loskutoff et al., Biery et al. or Bondioli et al. in order to obtain transgenic cows capable of producing a human serum protein in their milk, with a reasonable expectation of success. Thus, the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Claims 122-127, newly added, are rejected under 35 U.S.C. 103 as being unpatentable over any one of Simons et al. (C38), Clark et al. (C35), Gordon et al. (C36) or Bremel et al. (C34), when taken with any one of Loskutoff et al. (C37), Biery et al. (C31) or Bondioli et al. (C32), as applied to claims 73, 82, 83, 97 and 98-121 above, and further in view of First et al. ('979 patent).

At the time the claimed invention was made, First et al. had disclosed a method of in vitro fertilizing and culturing bovine ova into implantable embryos (see column 9, lines 59-63, for example). Accordingly, the additional modifications of the teachings of any one of Simons et al., Clark et al., Gordon et al. or Bremel et al. by employing bovine zygotes fertilized in vitro for gene transfer and subsequently culturing the transgenic bovine zygotes into implantable embryos would have been obvious to one of ordinary skill in the art. Thus, the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Any inquiry concerning this communication should be directed to Jasmine C. Chambers, Ph. D., at telephone number 703-308-2035.

Jasmine C. Chambers

JASEMINE C. CHAMBERS
PRIMARY EXAMINER
GROUP 1800